

PATENT  
USSN 10/087,473  
Docket 090/003c

### REMARKS

This paper is responsive to the Office Action dated May 4, 2004, which is the first action on the merits of the application.

Claims 1-22 were previously pending in the application; claims 1-20 were under examination. Upon entry of this Amendment, claims 3, 12, 16, and 19-22 are canceled without prejudice, and claims 23-29 are added. The added claims are believed to fall within the group under examination, and all the non-elected claims are cancelled. Accordingly, claims 1-2, 4-11, 13-15, 17-18, and 23-29 are now pending in the application and under examination.

Certain claims stand rejected under 35 USC §§ 102 and 103 in view of prior publications. Certain claims stand rejected for obviousness-type double patenting in view of some co-owned copending patent applications. Certain claims also stand rejected under 35 USC § 112 ¶ 2 with respect to the wording of the claims.

The claimed invention has been found to comply with the requirements of § 112 ¶ 1, for which applicant is grateful. Applicant also acknowledges with thanks confirmation that the information disclosed in the IDS has been considered by the Examiner.

Applicant understands that responsibility for this application has reverted to Examiner Thái-An N. Ton, Ph.D. Further consideration and allowance of the application is respectfully requested.

#### Interview summary:

The undersigned is grateful to Examiners Thái-An N. Ton, Joseph T. Weitach, and Deborah Crouch for the courtesy of an interview at the Patent Office on Thursday, September 2, 2004. Possible claim amendments and arguments were discussed that would help put the application in condition for allowance. This Response incorporates amendments and remarks discussed during the interview.

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Claim amendments:

Entry of the claim amendments does not introduce new matter into the disclosure. Support for the new claims may be found at various places in the specification, such as the following:

Claims 1 & 2: Page 19 lines 9-11; exemplified in Examples 3 and 5  
Claim 6: Page 5, lines 25-26  
Claims 23 to 28: Page 7, line 14 to page 8, line 15; exemplified in Example 3  
Claim 29: Claim 21 as previously presented.

These amendments are made to obtain coverage for certain aspects of the invention that are of current commercial interest. Applicant reserves the right to introduce claims to subject matter previously claimed or described in the disclosure in this or any other application.

Where no new limitations are added, coverage is maintained for all equivalents of the claimed subject matter for which applicant was previously entitled. Where new limitations have been introduced, coverage includes equivalents of the new limitations not previously claimed.

Double patenting:

Certain claims stand provisionally rejected for obviousness-type double patenting with respect to claims 12-15 and 35 of copending application USSN 10/039,956. Since the cited claims have been cancelled from the '956 application, this rejection no longer applies.

Certain claims stand provisionally rejected for obviousness-type double patenting with respect to claims 23-31 of copending parent application USSN 09/888,309. The claims of the '309 application were subject to a restriction requirement, dividing cell product claims from method claims. The product claims were elected for further prosecution, and the method claims are presently withdrawn. Applicant respectfully submits that there is currently no claim overlap between the two applications.

Certain claims stand provisionally rejected for obviousness-type double patenting with respect to claims in copending application USSN 09/994,440. This rejection is acknowledged. Applicant will file a terminal disclaimer in one of the applications or otherwise address this issue once the Office and the applicant agree on what subject matter will be covered in each application.

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Rejections under 35 USC § 112 ¶ 2:

Claims 4, 5, and 7 are indicated in the Office Action as unclear for reasons of claim wording. The claims have now been amended, and applicant believes the new wording complies with the requirements of § 112 ¶ 2.

Rejections under 35 USC § 102:

Claim 19 stands rejected under § 102(b) with respect to an article by Bhatia et al., J. Exp. Med. 189:1139, 1999, relating to hematopoietic cells. Claims 19 and 20 stand rejected with respect to U.S. Patent No. 5,411,883 relating to neuron progenitor cells. The Office Action indicates that since claims 19 and 20 are product by process claims, the product is indistinguishable from what is in the cited references.

Applicant does not concede that the prior disclosures disclose or are enabling for the products previously covered by claims 19 and 20. Nevertheless, these claims have now voluntarily been cancelled. Applicant reserves the right to reintroduce claims to the same subject matter in this or any other application at a later time.

Rejections under 35 USC § 103:

Claims 1-10 and 12-20 stand rejected under 35 USC § 103(a) as being unpatentable over Thomson et al. (Proc. Natl. Acad. Sci. USA 92:7844, 1995) in view of U.S. Patent No. 5,851,832 (Weiss et al.). Claim 11 stands rejected under § 103 as unpatentable over Thomson et al. and Weiss et al., in combination with U.S. Patent No. 6,686,198 (Melton et al.). The Office Action indicates that the Thomson article teaches differentiating hES cells in gelatin-coated plates, and the Weiss patent teaches differentiating neural cells by culturing them on poly-ornithine treated glass or plastic.

Applicant respectfully disagrees. There is no motivation to combine the references in the manner cited. Furthermore, even when the references are combined, they do not enable the practice of the invention claimed here.

The Thomson paper generally describes the generation and characterization of primate embryonic stem cells, which are believed to be capable of making progeny of virtually any tissue type in an embryo. In contrast, the cells in the Weiss article are harvested from neural tissue, and are already committed to make progeny within the confines of the neuronal or glial families.

If embryonic stem cells are allowed to differentiate non-specifically as suggested in the Office Action, a highly muddled population of unremarkable cells emerges, with a heterogeneous spectrum

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of phenotypic markers. See Draper et al., J Anat. 200:249, 2002, the abstract of which is enclosed with this response. But this is hardly what is needed for in clinical therapy, drug screening, gene profiling, or many other sensible utilities. A patient being treated for spinal cord injury would not like the idea of being administered a mixture of neural cells, fibroblasts, cardiomyocytes, mesenchymal cells, hepatocytes, more fibroblasts, and some undifferentiated cells. A pharmaceutical company testing the toxicity of a potential small molecule drug will not like the idea of screening the drug with a mixture of hepatocytes, fibroblasts, neural cells, mesenchymal cells, cardiomyocytes, more fibroblasts, and some undifferentiated cells.

For this reason, it is highly desirable that populations of cells made from hES cells be relatively homogeneous cell type of interest. Because hES cells have a strong tendency to form mixed cell populations as described by Draper et al., it is important to develop paradigms capable of differentiating hES cells towards one cell type.

Traditionally, hES cells have been differentiated into cells of a particular lineage by first forming embryoid bodies. See U.S. Patent No. 6,602,711, col. 2, ¶ 2-4. The thinking is that when hES cells are assembled into embryoid bodies, there can be cross-talk between the cells that initiates and coordinates differentiation, enhancing emergence of pockets of relatively uniform cells.

The present application describes a new and alternative method for making homogeneous cell populations. Differentiation is initiated by abruptly plating undifferentiated cells onto a foreign surface (claim 1) or suddenly culturing them into a considerably altered medium. Without intending to be limited by theory, it is believed that the sudden change coordinates the differentiation process in a manner that directs them to differentiate into a particular lineage. The cell populations that emerge are surprisingly homogeneous. The virtues of this "direct differentiation" method are described throughout the specification, and illustrated in Example 3 (hepatocytes) and Example 5 (neural cells). The embodiments are unified by the use of a solid surface and an abrupt change in culture conditions, without the formation of embryoid bodies.

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The claims have been amended in a manner which is believed to focus the reader on the direct differentiation process, and the quality of the cell population that emerges. The cited references do not teach or suggest any aspect of the direct differentiation method. The Thomson patent does not teach or enable the formation of homogeneous cell populations. On the other hand, the cell populations of Weiss et al. are homogeneous neural cells before any culturing or further differentiation is performed. Either by themselves or in combination, the references do not teach or suggest how to take a population of pluripotent stem cells capable of differentiating into multiple lineages, and causing them to differentiate into a homogeneous fashion.

Thus, the claimed invention is novel and non-obvious over the prior art of record. Withdrawal of this rejection is respectfully requested.

Request for further Interview

Applicant respectfully requests that all outstanding rejections be reconsidered and withdrawn. The application is believed to be in condition for allowance, and a prompt Notice of Allowance is requested.

In the event that the Examiner determines that there are other matters to be addressed, applicant hereby requests an interview by telephone.

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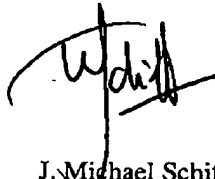
Fees Due

No fee is required with respect to the amendments to the claims, because the claim count has not changed.

Enclosed with this Amendment is authorization to charge the Deposit Account for the two month extension of time.

Should the Patent Office determine that a further extension of time or any other relief is required for further consideration of this application, applicant hereby petitions for such relief, and authorizes the Commissioner to charge the cost of such petitions and other fees due in connection with the filing of these papers to Deposit Account No. 07-1139, referencing the docket number indicated above.

Respectfully submitted,



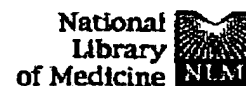
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September 15, 2004

Enclosures:

- J. Anat. 200:249, 2002: "Surface antigens of human embryonic stem cells: changes upon differentiation in culture." Draper, Pigott, Thomson & Andrews.
- U.S. Patent No. 6,607,211 B1: "Method of making embryoid bodies from primate embryonic stem cells." Thomson, Marshall & Swiergiel.



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1: J Anat. 2002 Mar;200(Pt 3):249-58.

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## Surface antigens of human embryonic stem cells: changes differentiation in culture.

Draper JS, Pigott C, Thomson JA, Andrews PW.

Department of Biomedical Science, University of Sheffield, UK.

We have analysed the surface antigen phenotype of a human embryonic (hES) cell line (H7) and the changes that occur upon differentiation in culture. The undifferentiated cells expressed Stage Specific Embryonic Antigens (SSEA3), SSEA4, TRA-1-60, and TRA-1-8 but not SSEA1. In these characteristics they closely resemble human embryonal carcinoma (EC) cells derived from testicular teratocarcinomas, and are distinct from murine ES cells. The undifferentiated cells also expressed the liver/bone/kidney isozyme of alkaline phosphatase detected by antibody TRA-2-54, the major histocompatibility antigens, HLA-ABC, and the human Thy1. Differentiation of hES cells was induced by retinoic acid, HMBA and with the appearance of various cell types including neurons and muscle. The surface antigens characteristically expressed by hES cells were down-regulated following induction of differentiation and other antigens appeared, notably several ganglioside glycolipids detected by antibodies VIN-1 (GD3 and GD2), VIN-2PB-22 (GD2), A2B5 (GT3) and ME311 (9-O-GD3). Whereas the expression of HLA was slightly down-regulated in differentiated cells, its expression was strongly induced by interferon- $\gamma$  in undifferentiated and the differentiated cells, although the induction in differentiated cultures was considerably stronger than in the stem cell cultures. These features of the human ES cells, and their pattern of differentiation, resembled the pluripotent human EC cell line NTERA-2 although the range of cells generated by the hES cells was considerably greater.

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